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SERIAL NUMBER 07/720,586	FILING DATE 06/28/91	FIRST NAMED INVENTOR MILLIMAN	ATTORNEY DOCKET NO. C 193/121
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SAXE, S	EXAMINER
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ART UNIT 1807	PAPER NUMBER 15
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DATE MAILED: 08/06/92

This Office communicates only the opinions of the Office of the Commissioner of Patents and Trademarks  
COMMISSIONER OF PATENTS AND TRADEMARKS

This application has been examined  Responsive to communication filed on 7/9/92  This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.  
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1.  Notice of References Cited by Examiner, PTO-892.
2.  Notice re Patent Drawing, PTO-948.
3.  Notice of Art Cited by Applicant, PTO-1449.
4.  Notice of Informal Patent Application, Form PTO-152
5.  Information on How to Effect Drawing Changes, PTO-1474.
6.  \_\_\_\_\_

Part II SUMMARY OF ACTION

1.  Claims 2, 3, 5, 7 - 23 are pending in the application.  
Of the above, claims \_\_\_\_\_ are withdrawn from consideration.
2.  Claims 1, 4, 6 have been cancelled.
3.  Claims \_\_\_\_\_ are allowed.
4.  Claims 2, 3, 5, 7 - 23 are rejected.
5.  Claims \_\_\_\_\_ are objected to.
6.  Claims \_\_\_\_\_ are subject to restriction or election requirement.
7.  This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8.  Formal drawings are required in response to this Office action.
9.  The corrected or substitute drawings have been received on \_\_\_\_\_. Under 37 C.F.R. 1.84 these drawings are  acceptable;  not acceptable (see explanation or Notice re Patent Drawing, PTO-948).
10.  The proposed additional or substitute sheet(s) of drawings, filed on \_\_\_\_\_, has (have) been  approved by the examiner;  disapproved by the examiner (see explanation).
11.  The proposed drawing correction, filed \_\_\_\_\_, has been  approved;  disapproved (see explanation).
12.  Acknowledgement is made of the claim for priority under U.S.C. 119. The certified copy has  been received  not been received  been filed in parent application, serial no. \_\_\_\_\_; filed on \_\_\_\_\_.
13.  Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14.  Other

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15. All of the objections and rejections made in Paper #11 have been overcome by the amendments and arguments made in Paper #14 filed on 7/9/92.

16. New objections and rejections, necessitated by the amendments to the original claims and the addition of new claims as set forth in Paper #14 filed on 7/9/92 are made below.

THE FOLLOWING ARE NEW GROUNDS OF OBJECTION AND REJECTION

17. The disclosure is objected to because of the following informalities:

- A. In claim 19, "selecting" should be "selected".
- B. SEQ ID Nos. are needed to identify the sequences in claims 8-14 and 19.
- C. In each of claims 15, 18 and 23 "streptococcus species group C" is listed twice.

Appropriate correction is required.

18. 35 U.S.C. § 101 reads as follows:

"Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title".

19. Amended claims 12-14 are rejected under 35 U.S.C. § 101

because the claimed invention is directed to non-statutory subject matter. Amended claims 12 and 13 are drawn to probe mixes consisting of sequences. A sequence is not a composition of matter. The claims should be rewritten to claim probe mixes consisting of oligonucleotides. Claim 14 is also rejected since it depends from claim 13.

20. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

21. Newly presented claim 15 and dependent claims 2, 3 and 5 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to Probe I. No other specific probes have been disclosed which meet the claim requirements. The specification does give guidance as to how to design such a probe. However this guidance is essentially useless in the absence of knowledge about the base sequence of rRNA or rDNA of *S. pyogenes*, and base sequence information on the rRNA or rDNA of other *Streptococcus* species would add to this usefulness. No information about base sequences of rRNA or rDNA is presented in the disclosure other than the three specifically

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mentioned oligonucleotides. In the absence of such information, one of ordinary skill in the art could "design" the probe of claim 15 only by randomly choosing base sequences and testing them. This would involve a huge effort. For example, the shortest of the three probes listed in the specification is 19 nucleotides in length. There are theoretically  $4^n$  or  $2.7 \times 10^{11}$  possible choices for a 19-mer. If the guidelines taught in the specification as to GC composition, self-complementarity, etc. are followed, this number will be decreased but will still be at least in the millions, if not billions. Thus in the absence of sequence data the disclosure is not enabling. See M.P.E.P. §§ 706.03(n) and 706.03(z).

Applicant has argued on pages 13-15 of Paper #14, filed on 7/9/92, against the 35 U.S.C. §112, first paragraph rejection of claim 1 which has been cancelled and replaced by newly presented claim 15. Applicant's argument is that the disclosure teaches how to design the claimed probes. However, one of ordinary skill in the art at the time of the invention would have known how to design probes (see, e.g., Wallace and Miyada Methods in Enzymology 152, 432-442 (1987)). The claim is not drawn to a method of knowing how to design probes, the claim is drawn to a probe. The invention is the probe. And as stated above, knowing how to design a probe is not enabling by itself for synthesis of a specific probe. Knowledge of base sequence is also necessary.

22. Newly presented claims 16 and 17 are rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a probe which distinguishes S. pyogenes from the Streptococcus species listed in Table I of the specification. Although the specification has presented data showing that there are probes which can distinguish S. pyogenes from the other Streptococcus species listed in Table I, there has been no evidence shown that these probes or any other probes will distinguish S. pyogenes from all other Streptococcus species. (Note: since claim 17 does not clearly state whether the probe will not hybridize to "some other" or "all other" Streptococcus species, the claim can be interpreted to mean "any other" which encompasses "all other" Streptococcus species.) The ATCC Catalogue of Bacteria & Bacteriophages (17th edition, 1989) lists 47 separate species of Streptococcus as well as several subgroups within species (see pages 207-212). The specification presents data for 14 separate species using the three probes which are disclosed. Although testing of these probes with the remaining 33 species would not require undue experimentation, it is not evident that any of the three disclosed probes will fulfill the requirement of the claim, i.e. that it will distinguish S. pyogenes from all other Streptococcus species. If none of these three probes does fulfill this requirement, it would require sequencing of the rRNA genes of many of the different Streptococcus species to find a probe which will distinguish S.

pyogenes from all other *Streptococcus* species, and such a probe may not even be possible. See M.P.E.P. §§ 706.03(n) and 706.03(z).

23. Newly presented claim 18 is rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to the three probe mix disclosed in the specification. As written the claim encompasses any probe mix which distinguishes *S. pyogenes* and *S. "equi"* from the other listed *Streptococcus* species. This would include not only probes complementary to rRNA but also probes to any other genes. Although guidance has been presented in the specification on the design of probes, as explained in Paragraph 21 of this Office action, the lack of information about base sequence composition of *Streptococcus* species prevents the claim from being enabled other than for the said three probe mix. See M.P.E.P. §§ 706.03(n) and 706.03(z).

24. Newly presented claim 23 is rejected under 35 U.S.C. § 112, first paragraph, as the disclosure is enabling only for claims limited to a method using 1, 2, or 3 of the 3 specifically disclosed probes or their complements. No evidence has been presented that any probes other than the said disclosed probes will hybridize to *S. pyogenes* rRNA and not to rRNA of the other listed *Streptococcus* species. In order to know if the method

will work with any other probes, one would need to randomly synthesize and test probes which would require a huge effort of trial and error or one would need to know the sequences of rRNA genes for the many species listed in the claim. This sequence data has not been disclosed and obtaining it would require a very large effort since rRNA of each species consists of 5S (about 120 bases in length), 16S (about 1400-1500 bases in length) and 23S (about 2900 bases in length). Because of the effort that would be required to develop probes to meet the claim requirements, the disclosure is not enabling for the method except for the specifically disclosed probes I, II and III and their complements. See M.P.E.P. §§ 706.03(n) and 706.03(z).

25. Claims 8-12 and 19-23 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Amended claim 11 is indefinite because the phrase "stringent hybridization conditions" has not been defined with the particularity necessary to make its meaning evident.

B. Amended claim 12 is indefinite because it has an improperly worded Markush group. The "and" (between the second and third sequences) should be an "or".

C. Newly presented claim 19 is confusing and indefinite. It claims a range "between 10 and 10 nucleotides". There is nothing

between "10 and 10". The claim also states "between 10 and 10 nucleotides, inclusive". How can a range be "between" two numbers and simultaneously be "inclusive" of the two numbers? Also the phrase "consisting essentially of" would broaden the limitation of "between".

D. Newly presented claims 20-22 are indefinite because of the phrase "essentially of between". "Between" would limit the claims whereas "essentially of" would broaden them.

E. Newly presented claim 23 is indefinite in using the phrase "able to" because the claim does not set forth under what conditions the probe is able to hybridize to S. pyogenes rRNA and not to rRNA of other Streptococcus species.

F. Claims 8-10 are indefinite because they depend from claim 6 which has been cancelled.

G. Claim 17 is vague because the meaning of "other" is not clear. Does "other" mean "some other" or "all other"?

26. Claims 2, 3, 5, 7 and 20-22 are rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

A. Claim 2 refers to a later claim (claim 15) rather than to an earlier claim. Claims 3 and 5 depend from claim 2 and are therefore also rejected.

B. Claim 2 fails to further restrict claim 15 since claim 15 already limits the probes to those which are complementary to

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rRNA or rDNA.

C. Claim 7 refers to a later claim (claim 19) rather than to an earlier claim.

D. Claims 20-22 broaden rather than limit claim 19. Because of the error in claim 19 stating a range of only "10 to 10", the broader ranges in claims 20-22 do not further limit claim 19.

27. Claim 19 lists 12 sequences. Only 3 of these are in the sequence listing. The other 9 do not constitute new matter but a new sequence listing as well as a computer readable form (CRF) which includes these sequences need to be submitted.

28. The documents submitted in the supplementary information disclosure statement (Paper #12, filed 3/4/92) were not all considered because four of them contained only every other page and one of them was also in French.

29. Applicant's amendment necessitated the new grounds of rejection. Accordingly, THIS ACTION IS MADE FINAL. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE

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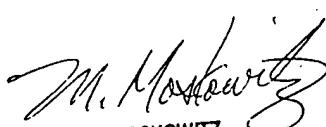
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ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Saxe whose telephone number is (703) 308-4235.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

31. Papers related to this application may be submitted to Group 180 by facsimile transmission. Papers should be faxed to Group 180 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4227.

  
MARGARET MOSKOWITZ  
SUPERVISORY PATENT EXAMINER  
GROUP 180

Stephen Saxe

August 4, 1992